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16. ABSTRACT

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PARATHION TOXICITY IN PERINATAL RATS BORN TO SPONTANEOUSLY HYPERTENSIVE DAMS

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Placental transfer and fetal toxicity of pesticides have been documented in normotensive rats but no reports appear in the literature regarding the susceptibility of spontaneously hypertensive (SHR) perinates to pesticide challenge. This report describes the effects of prolonged parathion exposure to perinatal rats born to hypertensive dams. Ninety day old, spontaneously hypertensive (WKY strain) male and female rats were bred and vaginal plugs were used to determine that copulation had occurred. Parathion (0.01, 0.10 and 1.00 mg/kg) suspended in peanut oil was administered daily to the dam via oral intubation from day one of gestation to day fifteen of lactation, a total of thirty-seven days. On day twenty-four post partum the perinates were examined. Male and female SHR perinates exhibited a significant reduction in plasma cholinesterase at the 1.00 mg/kg dose level. Changes in relative organ weights, hematological parameters and serum enzymes were found. Heart rate was significantly reduced at the 0.01 mg/kg and 0.10 mg/kg dose levels. The results of this study indicate that exposure of SHR dams to parathion during gestation and lactation resulted in toxicological effects in the perinate basically similar to those seen in normotensive perinates.

INTRODUCTION

Parathion is a broad spectrum organophosphate insecticide which is rendered toxic to insects and mammals upon oxidative desulfuration. The mode of action of organophosphorus insecticides is mainly through the inhibition of the enzyme acetylcholinesterase (AChE), an effect which has been observed in mammals (Diggle and Gage, 1951; Villeneuve *et al.*, 1971; Reiter *et. al.*, 1972; Talens and Woolley, 1973, and Teichert *et. al.*, 1976). The studies which show placental transfer of organophosphorus insecticides or their metabolites are Fish (1966), Ackerman and Engst (1970) and Harbison (1975).

The symptomology of organophosphate poisoning may vary in onset, severity and duration, depending on the route and magnitude of exposure. In instances of severe organophosphate poisoning alterations in hemato-

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logical parameters, including leucocytosis and altered differential leucocyte counts are evident (Namba, 1971). In instances of mild poisoning the manifestations are due to stimulation of parasympathetic nerve endings and visible signs include miosis, lacrimation and muscle fasciculations. Effects on the cardiac system are atrial fibrillation, conduction block, initial tachycardia and increased blood pressure followed by bradycardia and decreased blood pressure in the later stages of poisoning (Namba, 1971). Previous studies in our laboratory on the normotensive perinatal rat indicate that the cardiac system and vascular resistance may be altered by parathion administration (Deskin *et al.*, 1978).

These results suggest that organophosphate insecticides may further complicate or exaggerate human disease states which exhibit changes in heart function and blood pressure, for example, hypertension. The incidence of this disease has been increasing in this country in recent years. The spontaneous hypertensive rat (SHR) provides a useful model for studying a phenomenon analogous to essential hypertension in man (Okamoto and Aoki, 1963). The renin-angiotensin system (De Jong *et. al.*, 1972) and increased vascular resistance (Wellens *et al.*, 1975) have both been implicated in the development of spontaneous hypertension.

In this paper, we report the effect of parathion on perinatal rats born to spontaneously hypertensive dams which were dosed during gestation and lactation.

METHODS

Ninety-day old rats (WKY strain) were obtained from Taconic Farms, Germantown, New York. These rats were the offspring of successive generations of hypertensive animals obtained by brother-sister matings of animals selected for sustained high blood pressure. The rats were housed individually and were allowed to acclimate to the new surroundings for 1 week. After 1 week, one SHR male was placed in a cage with two SHR females for overnight. Vaginal plugs were used to determine whether copulation had occurred. The next day the dams were separated and were housed individually. Food and water were provided *ad libitum* with a light:dark cycle of 12:12.

Parathion[1] (99+ percent pure) was given in peanut oil by oral gavage at doses of 0.01, 0.10 and 1.00 mg/kg/day. The compound was administered from day 1 of gestation through 15 days of the lactation period. Peanut oil alone was administered to a control group. The total intubation volume did not exceed 2 ml per day. Fresh stock solutions were prepared weekly and were stored at 5°C.

At birth the number of pups born per litter was determined. On day 24 post-partum, five male and five female perinates from each dose group were randomly selected and examined for possible toxicological manifestations. After decapitation, relative organ weights were determined for the brain, heart, lungs, liver, stomach, intestines, spleen, kidneys, adrenals,

[1]Obtained from EPA Pesticide Repository, R.T.P., N.C.

TABLE 1. Relative Organ Weights of Perinatal Rats Born to Spontaneously Hypertensive Mothers Exposed to Parathion

Organ	Dose (mg/kg/day)			
	Control	0.01	0.10	1.00
Brain	0.04 ± 0.003[a]	0.04 ± 0.006	0.03 ± 0.004	0.03 ± 0.003
Heart	0.01 ± 0.003	0.006 ± 0.0004[b]	0.006 ± 0.0004[b]	0.005 ± 0.0002[b]
Lungs	0.01 ± 0.0009	0.01 ± 0.0009	0.01 ± 0.0009	0.009 ± 0.0008
Liver	0.05 ± 0.003	0.05 ± 0.001	0.05 ± 0.003	0.085 ± 0.001
Stomach	0.02 ± 0.002	0.02 ± 0.005	0.02 ± 0.004	0.03 ± 0.006
Intestine	0.10 ± 0.002	0.08 ± 0.004	0.11 ± 0.002	0.11 ± 0.004
Spleen	0.003 ± 0.0002	0.003 ± 0.0009	0.003 ± 0.0002	0.003 ± 0.0001
Kidney (combined)	0.015 ± 0.0009	0.015 ± 0.001	0.014 ± 0.0004	0.01 ± 0.0003[b]
Adrenals (combined)	0.0005 ± 0.0001	0.0005 ± 0.0001	0.0003 ± 0.0001	0.0004 ± 0.0001
Ovaries	0.002 ± 0.001	0.0006 ± 0.0001[b]	0.0008 ± 0.0002[b]	0.0007 ± 0.0002[b]
Testes	0.005 ± 0.001	0.005 ± 0.001	0.005 ± 0.001	0.006 ± 0.0009
Whole Body	32.0 ± 2.9	41.1 ± 4.2	42.0 ± 4.2	49.6 ± 5.4[b]

[a]Mean ± SEM.

[b]Significant compared to control ($p \leq 0.05$).

ovaries and testes. Complete blood cell counts, hemoglobin concentration, mean red blood cell volumes and hematocrits were analyzed. Blood smears were stained with Wright's stain and differential leucocyte counts were determined. Serum glutamic oxalic transaminase (SGOT) activity was assayed by the technique of Doumas and Biggs (1969). Creatine phosphokinase (CPK) activity was determined by the technique of Kornberg (1950). Plasma renin activity was measured by angiotensin I binding according to a radioimmunoassay procedure developed by Mallinckrodt Nuclear, St. Louis, Missouri. Red blood cell and plasma cholinesterase activities were measured by a pH stat method (Augustinsson, 1971). Perinates were anesthetized with sodium pentobarbital (45 mg/kg) and electrocardiograms were recorded with reference electrodes placed subcutaneously in both forelimbs, using the left leg as ground.

Results were analyzed by means of a Univac 1110 computer. Analysis of variance and regression analyses were performed with the Statistical Analysis System 72 (Barr *et al.*, 1972). The level of statistical significance was chosen as $p \leq 0.05$.

RESULTS

Relative organ weights of the SHR perinates are presented in Table 1. Whole body weights showed an increase with increasing dose of parathion, and were significantly increased over control values at the 1.00-mg/kg dose level. Heart weights were significantly reduced at parathion doses of 0.01 mg/kg and above. Kidney weights were significantly reduced at the 1.00-mg/kg dose level. Relative ovary weights showed a significant decline at doses of 0.01 mg/kg and above. No other organs examined showed any significant deviation from control values.

The effects of parathion on various hematological parameters are described in Table 2. With increasing dosage of parathion there was a significant increase in red blood cell counts at the 0.01- and 0.10-mg/kg dose levels, but not at the highest dose. An increase in white blood cell counts was also seen with significance noted at the 1.00-mg/kg dose

TABLE 2. The Effects of Parathion on Hematological Parameters of Perinatal Rats

Dose (mg/kg/day)	Red Cell Count (10^6 cells/mm^3)	White Cell Count (10^3 cells/mm^3)	Hemoglobin (gm %)	Mean Cell Volume (μ^3)	Hematocrit (%)
Control	4.3 ± 0.18[a]	3.3 ± 0.29	10.5 ± 0.40	76.5 ± 2.10	31.2 ± 0.80
0.01	6.0 ± 0.38[b]	3.7 ± 0.45	12.6 ± 0.80[b]	66.2 ± 2.10	40.9 ± 1.10
0.10	5.4 ± 0.21[b]	4.2 ± 0.42	13.5 ± 0.80[b]	59.3 ± 2.50[b]	45.7 ± 1.40
1.00	4.2 ± 0.31	5.2 ± 0.46[b]	11.3 ± 0.60	50.1 ± 2.30[b]	21.7 ± 2.70

[a]Mean ± SEM.

[b]Significant compared to control ($p \leq 0.05$).

TABLE 3. The Effects of Parathion on Differential Leucocyte Counts

Dose (mg/kg/day)	Leucocyte				
	Basophil	Eosinophil	Neutrophil	Lumphocyte	Monocyte
	(Percent of Total Leucocyte Count)				
Control	0.3 ± 0.1[a]	1.5 ± 0.6	19.7 ± 1.0	68.2 ± 4.9	5.5 ± 0.8
1.00	0.6 ± 0.2	0.9 ± 0.3	33.2 ± 1.5[b]	60.0 ± 1.6	9.9 ± 1.4[b]

[a]Mean ± SEM.

[b]Significant compared to control ($p \leq 0.05$).

level. Parathion in doses of 0.01- and 0.10-mg/kg caused a significant elevation of hemoglobin concentration in the SHR perinates. Mean cell volumes were significantly depressed as the dose of parathion was increased to 0.10- and 1.00-mg/kg. Parathion administration had no effect on hematocrit.

Table 3 summarizes the effect of parathion on differential leucocyte counts. Only perinates receiving 1.00-mg/kg parathion and control perinates were examined. Perinates born to dams receiving 1.00-mg/kg parathion showed significant increases in percent neutrophils and monocytes. Percent basophils, eosinophils and lymphocytes were not significantly altered by parathion.

The effect of parathion on SGOT activity is described in Table 4. A dose-related increase in SGOT activity was seen at the 1.00-mg/kg dose level. CPK activity (Table 4) showed a significant increase at the 1.00-mg/kg dose level. The SHR perinates showed a significant increase in plasma renin activity at the 0.01- and 1.00-mg/kg dose levels (Table 4).

TABLE 4. The Effects of Parathion on Serum Glutamic Oxalic Transaminase, Creatine Phosphokinase and Plasma Renin Activities

Dose (mg/kg/day)	Enzyme		
	SGOT (IU/L)	CPK (IU/L)	Plasma Renin (ng/ml/hr)
Control	359 ± 25.9[a]	2533 ± 63.4	1.1 ± 0.3
0.01	386 ± 22.3	2797 ± 102.8	2.5 ± 0.2[b]
0.10	408 ± 21.4	2751 ± 152.2	1.0 ± 0.04
1.00	410 ± 10.2[b]	2887 ± 90.6[b]	2.3 ± 0.2[b]

[a]Mean ± SEM.

[b]Significant compared to control ($p \leq 0.05$).

Male SHR perinates exhibited a significant reduction in both red blood cell and plasma cholinesterase activities at the 1.00-mg/kg dose level (Table 5). Female SHR perinates exhibited a significant reduction in plasma cholinesterase activities at the 1.00-mg/kg dose level and exhibited a numerical reduction in red blood cell cholinesterase with increased dose of parathion. AChE activity in the dams was unaffected by the dosing regime.

Parathion caused no significant reduction in the number of pups born per litter nor was the survival rate to day 24 post partum of the perinates born to the SHR dams altered by parathion administration (Table 6). Exposure of SHR dams to parathion at the 0.01- and 0.10-mg/kg dose levels resulted in a significant reduction of heart rate of the pups (Table 7). Ventricular depolarization (QRS complex duration), ventricular repolarization (S-T interval), atrial depolarization (P-R interval) and ventricular depolarization plus repolarization (Q-T interval) were not significantly altered by parathion administration (Table 7).

DISCUSSION

In the literature, the extent of placental transfer and the degree of poisoning by an organophosphate insecticide are usually measured by the degree of cholinesterase inhibition. The work of Villeneuve *et al.* (1971), Reiter *et al.* (1972) and Talens and Woolley (1973) confirms the inhibition of AChE in perinates by administration of parathion to dams. The results obtained from this study indicate that the administration of 1.00-mg/kg of parathion to SHR dams was sufficient to cause about 37 percent plasma AChE inhibition in the perinates. However, pesticide administration to the

TABLE 5. The Effects of Parathion on Red Blood Cell and Plasma Cholinesterase Activity

Dose (mg/kg/day)	Red Blood Cells		
	Male	Female	Mother
Control	2.33 ± 0.21[a]	2.04 ± 0.27	2.88 ± 0.24
0.01	2.31 ± 0.41	1.78 ± 0.27	2.14 ± 0.22
0.10	2.00 ± 0.25	1.89 ± 0.19	2.24 ± 0.15
1.00	1.69 ± 0.01[b]	1.68 ± 0.02	2.51 ± 0.19
Dose (mg/kg/day)	**Plasma**		
	Male	Female	Mother
Control	1.25 ± 0.06	1.23 ± 0.06	1.08 ± 0.08
0.01	0.74 ± 0.05[b]	1.00 ± 0.14	0.95 ± 0.03
0.10	0.98 ± 0.04	1.08 ± 0.05	0.80 ± 0.02
1.00	0.78 ± 0.07[b]	0.79 ± 0.03[b]	0.79 ± 0.08

[a]Mean ± SEM expressed as micromoles of acetylcholine perchlorate hydrolyzed/min/ml of plasma or packed red cells.

[b]Significant compared to control ($p \leq 0.05$).

dams for the 37-day period caused no visible clinical signs of poisoning and did not alter AChE activities in the dams. This observation is consistent with results indicating that parathion toxicity is greater in young rats (Brodeur and Dubois, 1963; Dubois, 197l; Alary and Brodeur, 1970) and that sexual maturity affords protection against the toxicity of parathion (Swann *et al.*, 1958). The decrease in male plasma AChE at the 0.01-mg/kg dose level (Table 5) may be a result of normal biological variation.

Similar to the results of Namba (1971), leucocytosis was noted in the SHR perinates. In instances of severe organophosphate poisoning Namba (1971) reported an increase in the percentage of neutrophils with a reduction in the percentages of lymphocytes and monocytes. The results of this study bear out the increase in the percent of neutrophils and a non-significant decrease in the percent of lymphocytes. However, the percent of monocytes showed an increase. The difference is probably due to the different route of exposure and the length of exposure. The statistical significance noted in red blood cell count and hemoglobin concentration may be due to simple biological variation or may be real. Additional work will be required to substantiate these findings.

In screening for instances of myocardial infarction (MI), an enzyme profile of SGOT, CPK and LDH (lactic dehydrogenase) is commonly used. Elevated levels of SGOT have been implicated in instances of liver necrosis and hepatitis. Liver tissue is rich in both GOT and GPT (glutamic pyruvic transaminase), but it contains more GPT than GOT. Therefore GPT is a more specific indicator of liver damage, and GOT is a specific indicator of cardiac necrosis (Harper, 1975). CPK levels are increased in conditions other than those associated with muscle injury or disease; for example, elevated levels have been demonstrated following vigorous exertion (Griffiths, 1966). CPK activity is also related to thyroid function (Graig and Smith, 1965). These diverse conditions associated with increased CPK activity are not likely to be a source of confusion when the procedure is used for the evaluation of suspected MI (Crowley, 1968).

The renin-angiotensin system is intricately involved in the homeostasis of peripheral vascular resistance. The studies of Sinaiko and Mirkin (1974), Sen *et al.* (1972) and De Jong *et al.* (1972) suggest that the renin-angiotensin system may be important in the development of spontaneous hypertension. The SHR perinates in this study exhibited a significant elevation in plasma renin activity at the 0.01- and 1.00-mg/kg dose levels. The significance noted at the 0.01-mg/kg dose level may be the result of normal biological variation. This result lends skepticism to the finding at the 1.0-mg/kg dose level. These findings may be real or may result from assay reproductibility or may be due to normal biological variability. Further work in this area will be required before a complete understanding is reached.

Electrocardiographic diagnosis of myocardial infarctions include S-T segment elevation, increased QRS complex duration and axis deviation. Although none of these changes were manifest, decreased heart rate was noted. Parasympathetic stimulation has classically been known to cause a

slowed heart rate with a decrease behind the atrial beat. Although only a sparse amount of data is available, it suggests that organophosphorus poisons promote the development of hypercoagulation (Maksimov, 1974). This may account for the alteration of the blood supply to the myocardium, which is the causative agent in MI. Here again a transient increase in heart rate lends one to believe that what we are seeing is normal biological variation. Further investigation is needed to substantiate these findings.

In summary the results of this study indicate that exposure of pregnant spontaneously hypertensive female rats (WKY strain) to parathion during gestation and lactation resulted in indirect toxicological effects in the developing fetus similar to those seen in normotensive perinates exposed in a similar manner. Red blood cell and plasma cholinesterase were inhibited in the perinates but were unaffected in the dams. Blood paramaters were altered indicating exposure. Organ involvement was seen, the most notable being a 50 percent reduction in heart weight at the high dose level. The serum enzymes SGOT and CPK showed signs of being altered. The renin-angiotensin system showed signs of alteration. No gross cardiac changes were apparent, although heart rate was altered. Perinates born to SHR dams may or may not be more susceptible to

TABLE 6. Litter Size and Survival Rate of Rats Born to Spontaneously Hypertensive Dams

Dose (mg/kg/day)	No. Pups Born Per Litter	Survival Rate to Day 24 (% of Total Born)
Control	9.3 ± 0.62[a]	76
0.01	7.9 ± 1.13	73
0.10	8.0 ± 1.10	49
1.00	8.3 ± 1.16	76

[a]Mean ± SEM.

TABLE 7. Electrocardiographic Data Obtained from Perinatal Rats Born to Spontaneously Hypertensive Dams

		Interval		
Dose (mg/kg/day)	Heart Rate (Beats/min.)	QRS Duration	S-T (Expressed in Milliseconds)	P-R
Control	339 ± 8[a]	80 ± 6	50 ± 4	50 ± 3
0.01	294 ± 19[b]	80 ± 8	50 ± 7	50 ± 7
0.10	274 ± 16[b]	70 ± 5	50 ± 4	30 ± 3
1.00	387 ± 9	80 ± 04	40 ± 2	50 ± 4

[a]Mean ± SEM.

[b]Significant compared to control ($p \leq 0.05$).

parathion exposure, but additional work is required to elucidate this. In addition to examining AChE activity additional parameters which are indicative of cardiac function need be examined in hypertensive animals.

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